

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.: 10/664,037 Confirmation No.: 2610
Applicant(s): Guarino *et al.*
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Art Unit: 1657
Examiner: Vera Afremova
Title: ENVIRONMENTS THAT MAINTAIN FUNCTION OF
PRIMARY LIVER CELLS

Docket No.: 035510/305985(P-6186)
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REPLY BRIEF UNDER 37 C.F.R. § 41.41(a)(1)

This Reply Brief is filed pursuant to 37 CFR § 41.41(a)(1) and is filed in response to the Examiner's Answer of July 11, 2007, the Examiner's Answer being in response to an Appeal Brief filed March 2, 2007.

Claim Rejections – 35 U.S.C. § 103

Claims 1-3, 6-8, 10, 12-16, 58, and 61-67 stand rejected under 35 U.S.C. § 103(a) as being obvious in light of published International Application WO 98/56897 (the '897 application), U.S. Patent No. 6,562,616 (the '616 patent) and U.S. Patent No. 5,942,436 (the '436 patent), in view of U.S. Patent No. 6,653,105 (the '105 patent) and published Japanese Application JP 04322657 (the '657 application). Appellants maintain their traversal of this rejection and submit that the Examiner has not used the correct standard while applying the statutory language of 35 U.S.C. § 103(a). This reply will focus on the correct standard to be used and how Appellants have met the proper standard.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), set out the framework for applying the statutory language of § 103:

1. Determining the scope and content of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering any relevant secondary considerations.

The '897 application discloses a method for culturing primary porcine liver cells by incubating the cells in plastic dishes including culture medium, HYAFF matrices (esters of hyaluronic acid with benzyl alcohol) and dermal fibroblasts (page 13, lines 5-20). The '616 patent discloses a two-compartment, parallel-plate bioreactor with an internal membrane oxygenator in which hepatocytes cultured on glass slides coated with type I collagen are maintained (column 24, lines 52-54 and column 25, lines 16-30 and 55-57). The '436 patent discloses a method for culturing primary liver cells such as rat hepatocytes and human hepatocytes in culture vessels coated with type I collagen (column 4, lines 36-45). As the Examiner has acknowledged, the '897 application, the '616 patent and the '436 patent are "lacking particular disclosure about the use of polycationic polymer or poly-L-ornithine in the surface coating composition in the method for culturing liver cells" (Examiner's Answer, page 6, lines 1-2).

The '105 patent teaches that polybasic amino acids, such as polyornithine and polylysine, and extracellular matrix proteins, such as laminin, collagen and fibronectin, can be used as components of a surface coating composition for enhancing the growth of serum-free C3A cells (column 6, lines 10-24). The clonally derived, serum-free C3A cell line "retains most of the characteristics of the human hepatocyte parent C3A line" (column 4, lines 5-7). The '657 application teaches that a cell culture surface "on which many fine protrusions and groves are formed is brought into contact with cells or a tissue(s) selected from connective tissues and nerve, glia, Schwann, skin, muscle, kidney and liver cells" (English abstract). The '657 application further teaches that "one or a mixture of collagen, poly-L-lysine, poly-L-ornithine, laminin, fibronectin, [ch]ick plasma, artificial lipid films ... and nerve growth factors" can be adhered to the cell culture surface (English abstract). The Examiner maintains that it "would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to add poly-L-ornithine taught by [the '105 patent and the '657 application] to the coating polymer compositions of [the '897 application, the '616 patent and/or the '436 patent] with a

reasonable expectation of success in culturing liver cells because the cell attachment surfaces comprising poly-L-ornithine and collagen type I have been taught and/or suggested by the prior art of attaching, incubating and growing hepatocytes as adequately demonstrated by the cited reference combined” (Examiner’s Answer, page 6, lines 10-16). As previously made of record, Appellants respectfully disagree with this conclusion.

As discussed herein, the ‘105 patent teaches that polybasic amino acids, such as polyornithine and polylysine, and extracellular matrix proteins, such as laminin, collagen and fibronectin, can be used as components of a surface coating composition for enhancing the growth of serum-free C3A cells. The **clonally derived**, serum-free C3A cells (and the human hepatocyte parent C3A line from which they are derived) are not **primary liver cells** (*i.e.*, hepatocytes isolated directly from liver tissue), but rather an established human hepatocyte line. As is well known to one of ordinary skill in the art, the requirements for culturing primary liver cells are significantly different from those required for culturing an established hepatocyte line. As also discussed herein, the ‘657 application teaches that a cell culture surface having fine protrusions and groves and coated with **one or a mixture of a laundry list of substances** (*i.e.*, collagen, poly-L-lysine, poly-L-ornithine, laminin, fibronectin, chick plasma, artificial lipid films, and nerve growth factors) can be used to culture **a variety of cells and tissues**, including connective tissues and nerve, glia, Schwann, skin, muscle, kidney and liver cells. Accordingly, Appellants submit that substantial differences exist between the disclosures of the ‘105 patent and the ‘657 application regarding the culturing of established hepatocytes in serum-free media or the culturing of various cells/tissues on textured surfaces in the presence of a variety of substances, and the methods recited in claims 1-3, 6-8, 10, 12-16, 58, and 61-67 for culturing **primary liver cells**.

Furthermore, although the U.S. Supreme Court recently declined to permit a “rigid” application of the teaching-suggestion-motivation to combine test to obviousness determinations, the Court did hold that the presence or absence of a teaching, suggestion or motivation to combine the cited references provides a “helpful insight” regarding the obviousness of an invention. *KSR Int’l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1731 (2007). In the instant case, Appellants submit that no such helpful insight exists. Contrary to the Examiner’s assertions,

nothing in the '897 application, the '616 patent, the '436 patent, the '105 patent, or the '657 application provides a reason for the skilled artisan to combine their teachings to arrive at Appellants' methods for culturing primary liver cells. At most, the combination of these five references serves as an invitation to experiment with multiple parameters (*e.g.*, various support surfaces and a variety of coating compositions) to ascertain their suitability in methods for culturing a variety of cell and tissue types. Yet an invitation to experiment is not sufficient grounds to reject an invention as obvious. One of skill in the art at the time of the invention would not have had sufficient guidance to have a reasonable expectation of success in combining the teachings of the '897 application, the '616 patent, the '436 patent, the '105 patent, and the '657 application to arrive at Appellants' claimed invention. Where the prior art gives only general guidance as to the particular form of the invention or how to achieve it, as here, obviousness may not be found. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81, 90-91 (Fed. Cir. 1986).

Moreover, in *KSR*, the Supreme Court went on to acknowledge the importance in making obviousness determinations of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in way the claimed invention does." *KSR*, 127 S. Ct. at 1731. In the instant case, the Examiner has attempted to piece together the claimed invention by citing multiple (*i.e.*, five) references that teach various elements of the claims. Contrary to the Examiner's assertion, these five references do not all "seek to solve the same problems as the instant application and claims" (Examiner's Answer, page 6, line 20). Rather, as discussed herein, these references are directed to the culturing of various cells and tissues on a variety of surfaces in the presence of various substances. Given the lack of evidence of a reason to combine the references, it appears that the Examiner has engaged in impermissible "hindsight reconstruction" in formulating the present rejection. See, *Graham*, 383 U.S. at 36 (stating the importance of guarding against "slipping into hindsight and...resisting [the] temptation to read into the prior art the teachings of the invention in issue"). Therefore, in establishing obviousness, it is improper "to use the claimed invention as an instruction manual or template to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). Accordingly, the lack of a

bona fide reason to combine the cited references to arrive at the claimed methods for culturing primary liver cells provides further evidence that the pending claims are not obvious.

In summary, “[t]o reach a proper conclusion under §103, the decisionmaker must step backward in time and into the shoes worn by [a person having ordinary skill in the art] when the invention was unknown and just before it was made. In light of *all* the evidence, the decisionmaker must then determine whether . . . the claimed invention as a whole would have been obvious at *that* time to *that* person” (emphasis in the original). *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Appellants maintain that the Examiner has impermissibly used the claims as an instruction manual to find prior art that might render the claims obvious, rather than addressing the question of whether it would have been obvious to combine the ‘897 application, the ‘616 patent, the ‘436 patent, the ‘105 patent, and the ‘657 application without having access to the instant application to arrive at the claimed invention as a whole. As stated by the Federal Circuit,

[A]lthough *Graham v. John Deere Co.*, 383 U.S. at 17, 148 USPQ at 476, requires that certain factual inquiries, among them the differences between the prior art and the claimed invention, be conducted to support a determination of the issue of obviousness, the actual determination of the issue requires an evaluation in the light of the findings in those inquiries of the obviousness of **the claimed invention as whole**, not merely the differences between the claimed invention and the prior art.

Lear Siegler, Inc. v. Aeroquip Corp., 733 F.2d 881, 221 USPQ 1025, 1033 (Fed. Cir. 1984) (emphasis added). Thus, Appellants submit that a *prima facie* case of obviousness under 35 U.S.C. § 103(a) has not been established and respectfully request that the rejection of claims 1-3, 6-8, 10, 12-16, 58, and 61-67 be overturned.

Claims 10, 58 and 65-67 Should Be Considered Separately

Claims 10, 58 and 65-67 contain limitations requiring that collagen I and poly-L-ornithine be bound to the CAR material, where the CAR material, the collagen I and the poly-L-ornithine thereby form a cell adhesion promoting surface for culturing primary liver cells.

Appellants submit that claims 1-3, 6-8, 10, 12-16, 58, and 61-67 are non-obvious over the '897 application, the '616 patent and the '436 patent, in view of the '105 patent and the '657 application for the reasons discussed above. However, should the Board disagree, claims requiring that collagen I and poly-L-ornithine be bound to the CAR material (*i.e.*, claims 10, 58 and 65-67) are narrower in scope and thus should be considered separately in view of the arguments presented above.

Specifically, the teachings of the '105 patent that polybasic amino acids and ECM proteins can be used to enhance growth of an established hepatocyte line, and of the '657 application that multiple cell and tissue types can be cultured on grooved surfaces coated with one or more of a laundry list of substances, do not guide the skilled artisan in arriving at Appellants' specific method for culturing **primary liver cells**, comprising providing a cell adhesion promoting surface including a CAR material, collagen I and poly-L-ornithine. Rather, the impermissible combination of the teachings of these two references with the disclosures of the '897 application, the '616 patent and the '436 patent merely invite experimentation, and, as discussed herein, an invitation to experiment is not sufficient grounds to reject an invention as obvious.

CONCLUSION

Appellants maintain that the Examiner has failed to carry her burden of establishing that the claims are not patentable because she has failed to establish that the claims are *prima facie* obvious. Accordingly, claims 1-3, 6-8, 10, 12-16, 58, and 61-67 are allowable. For these reasons, presented in detail above, Appellants respectfully request that the rejection be overturned.

It is not believed that extensions of time are required. However, in the event that extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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